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SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

Accoran 6 mg/ml (Concentrate for solution for infusion)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml of concentrate contains 6 mg of busulfan. Each 10 ml vial contains 60 mg of busulfan.

After dilution: 1 ml of solution contains 0,5 mg of busulfan

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Concentrate for solution for infusion.

A clear, colourless solution free from visible particles.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Conditioning treatment prior to haematopoietic progenitor cell transplantation in adults when the combination of busulfan and cyclophosphamide (Bu/Cy2) is considered the best available option.

4.2 Posology and method of administration

Posology

Accoran should not be given by rapid IV injection or bolus.

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Accoran should be administered under the supervision of a qualified medical practitioner who is experienced in conditioning treatment prior to haematopoietic progenitor cell transplantation, in the use of cancer chemotherapeutic agents and in the management of patients with severe pancytopenia.

It is recommended to use actual body weight for dosing.

All patients should be pre-medicated with anticonvulsant medicine to prevent seizures reported with the use of high dose Accoran. Anti-emetics should be administered prior to the first dose and continued on a fixed schedule through its administration.

The recommended dose and schedule of administration is:

0,8 mg/kg body weight (BW) of Accoran as a two-hour infusion every 6 hours over 4 consecutive days for a total of 16 doses, prior to haematopoietic progenitor cell transplantation (HPCT).

Obese patients:

For obese or severely obese patients, dosing based on adjusted ideal body weight (AIBW) could be considered. Ideal body weight (IBW) should be calculated as follows (height in cm and weight in kg):

IBW (kg; men) = 50 + 0,91 X (height - 152); IBW (kg; women) = 45 + 0,91 X (height-152).

Adjusted ideal body weight (AIBW) should be calculated as follows:

AIBW = IBW + 0,25 X (actual body weight - IBW)

Paediatric population

The safety and efficacy of Accoran in children have not been established.

Method of administration

Accoran must be diluted before administration. A final concentration of approximately 0,5 mg/ml busulfan should be achieved (see below). Accoran should be administered by IV infusion via central venous catheter.

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For instructions on dilution see section 6.6.

4.3 Contraindications

- Hypersensitivity to busulfan or to any of the excipients listed (see section 6.1)
- Pregnancy and lactation (see section 4.6)
- The safety and efficacy in children have not been established
- Hepatic insufficiency

4.4 Special warnings and precautions for use

The consequence of treatment with Accoran is profound myelosuppression, occurring in all patients. Severe granulocytopenia, thrombocytopenia, anaemia, or any combination thereof may develop. Frequent complete blood counts, including differential white blood cell counts, and quantitative platelet counts should be monitored during the treatment and until recovery is achieved.

Prophylactic use of anti-infective agents should be considered for the prevention and management of infections during the neutropenic period. Platelet and red blood cell support, as well as use of growth factors such as granulocyte colony stimulating factor (G-CSF), should be used as indicated.

In adults absolute neutrophil counts < 0,5 X 10^9 /l at a median of 4 days post-transplant occurred in 100 % of patients and recovered at median day 10 and 13 days following autologous and allogenic transplant respectively (median neutropenic period of 6 and 9 days respectively). Thrombocytopenia (< 25 x 10^9 or requiring platelet transfusion) occurred at a median of 5-6 days in 98 % of patients. Anaemia (haemoglobin< 8,0 g/dl) occurred in 69 % of patients.

Hepatic impairment:

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Accoran has not been studied in patients with hepatic impairment. Since busulfan is mainly metabolised through the liver, caution should be observed when busulfan is used in patients with pre-existing impairment of liver function, especially in those with severe hepatic impairment. It is recommended when treating patients with Accoran that serum transaminase, alkaline phosphatase, and bilirubin should be monitored regularly 28 days following transplant for early detection of hepatotoxicity.

Hepatic veno-occlusive disease is a major complication that can occur during treatment with busulfan. Patients who have received prior radiation therapy, greater than or equal to three cycles of chemotherapy, or prior progenitor cell transplant may be at an increased risk (see section 4.8).

As documented in clinical studies, no treated patients experienced cardiac tamponade or other specific cardiac toxicities related to busulfan. However cardiac function should be monitored regularly in patients receiving busulfan (see section 4.8).

Occurrence of acute respiratory distress syndrome with subsequent respiratory failure associated with interstitial pulmonary fibrosis was reported in busulfan studies in one patient who died, although, no clear aetiology was identified. In addition, busulfan might induce pulmonary toxicity that may be additive to the effects produced by other cytotoxic agents. Therefore, attention should be paid to this pulmonary issue in patients with prior history of mediastinal or pulmonary radiation (see section 4.8).

Periodic monitoring of renal function should be considered during therapy with busulfan (see section 4.8).

Seizures have been reported with high dose busulfan treatment. Special caution should be exercised when administering the recommended dose of busulfan to patients with a history of seizures. Patients should receive adequate anticonvulsant prophylaxis. In adults and children studies, data with busulfan were obtained when

using concomitant administration of either phenytoin or benzodiazepines for seizure prophylaxis. The effect of those anticonvulsant agents on busulfan pharmacokinetics was investigated in a phase II study (see section 4.5).

The increased risk of a second malignancy should be explained to the patient. Leukaemia patients treated with busulfan developed many different cytological abnormalities, and some developed carcinomas. Busulfan is thought to be leukaemogenic.

Fertility

Busulfan can impair fertility. Therefore, men treated with busulfan are advised not to father a child during and up to 6 months after treatment and to seek advice on cryo-conservation of sperm prior to treatment because of the possibility of irreversible infertility due to therapy with busulfan. Ovarian suppression and amenorrhoea with menopausal symptoms commonly occur in pre-menopausal patients. Impotence, sterility, azoospermia, and testicular atrophy have been reported in male patients. The solvent dimethylacetamide (DMA) may also impair fertility. DMA decreases fertility in male and female rodents (see sections 4.6 and 5.3).

Cases of thrombotic microangiopathy after hematopoietic cell transplantation (HCT), including fatal cases, have been reported in high-dose conditioning regimens in which busulfan was administered in combination with another conditioning treatment.

4.5 Interaction with other medicinal products and other forms of interaction

Administration of itraconazole to patients receiving high-dose busulfan may result in reduced busulfan clearance. Also, there are published case reports of increased plasma levels of busulfan after administration of metronidazole. Patients who are concurrently treated with busulfan and itraconazole or metronidazole should be closely monitored for signs of busulfan toxicity.

No interaction was observed when busulfan was combined with fluconazole (antifungal agent).

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Ketobemidone (analgesic) might be associated with high levels of plasma busulfan. Therefore special care is recommended when combining these two compounds.

In adults, for the BuCy2 regimen it has been reported that the time interval between the last oral busulfan administration and the first cyclophosphamide administration may influence the development of toxicities. A reduced incidence of Hepatic Veno Occlusive Disease (HVOD) and other regimen-related toxicity has been observed in patients when the lag time between the last dose of oral busulfan and the first dose of cyclophosphamide is > 24hours.

Paracetamol is described to decrease glutathione levels in blood and tissues, and may therefore decrease busulfan clearance when used in combination (see section 4.4).
Caution should be exercised when using paracetamol prior to (less than 72 hours) or concurrently with busulfan due to a possible decrease in the metabolism of busulfan.

Either phenytoin or benzodiazepines were administered for seizure prophylaxis in patients participating to the clinical trials conducted with intravenous busulfan (see section 4.2 and 4.4).

The concomitant systemic administration of phenytoin to patients receiving high-dose of oral busulfan has been reported to increase busulfan clearance, due to induction of glutathion-S-transferase whereas no interaction has been reported when benzodiazepines such as diazepam, clonazepam or lorazepam have been used to prevent seizures with high-dose busulfan.

No evidence of an induction effect of phenytoin has been seen on busulfan data. A phase II clinical trial was performed to evaluate the influence of seizure prophylaxis treatment on intravenous busulfan pharmacokinetics. In this study, 24 adult patients received clonazepam (0,025-0,03 mg/kg/day as IV continuous infusions) as

anticonvulsant therapy and the PK data of these patients were compared to historical data collected in patients treated with phenytoin. The analysis of data through a population pharmacokinetic method indicated no difference on intravenous busulfan clearance between phenytoin and clonazepam based therapy and therefore similar busulfan plasma exposures were achieved whatever the type of seizure prophylaxis.

No interaction was observed when busulfan was combined with 5 HT_3 antiemetics such as ondansetron or granisetron.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential/contraception

Women of childbearing potential must use effective methods of contraception both before and during and up to 6 months after treatment.

Pregnancy

Accoran is contraindicated during pregnancy. Studies in animals have shown reproductive toxicity (embryo-foetal lethality and malformations). (see section 5.3)

Breast-feeding

It is not known whether busulfan and DMA are excreted in breast milk. Because of the potential for tumorigenicity shown for Accoran, breastfeeding should be discontinued during treatment with Accoran.

Fertility

Busulfan and DMA can impair fertility. Therefore, men treated with Accoran is advised not to father a child during and up to 6 months after treatment with Accoran. It is recommended to seek advice on cryo-conservation of sperm prior to treatment because of the possibility of irreversible infertility (see section 4.4).

4.7 Effects on ability to drive and use machines

Accoran may have an influence on the ability to drive a vehicle and use machines. It may cause dizziness. Therefore, patients must be cautious when driving or using machines and should be advised not to drive or operate machinery if they experience these symptoms (see section 4.8).

4.8 Undesirable effects

Summary of the safety profile

Busulfan in combination with cyclophosphamide

Serious toxicities involving the haematologic, hepatic and respiratory systems were considered as expected consequences of the conditioning regimen and transplant process. These include infection and Graft-versus host disease (GVHD) which although not directly related, were the major causes of morbidity and mortality, especially in allogeneic HPCT.

Blood and lymphatic system disorders:

Myelo-suppression and immuno-suppression were the desired therapeutic effects of the conditioning regimen. Therefore all patients experienced profound cytopenia: leucopenia, thrombocytopenia and anaemia.

Immune system disorders

Cases of graft versus host disease of varying severity have been observed in clinical studies.

Infections and infestations

Episodes of infection have been reported, including fatal or life threatening cases of pneumonia. Most cases of fever and chills were graded as mild/moderate.

Hepato-biliary disorders

Serious adverse events have included reports of liver toxicity. HVOD is a recognised potential complication of conditioning therapy post-transplant. Elevated bilirubin and AST levels have also been reported.

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Respiratory, thoracic and mediastinal disorders:

One patient experienced a fatal case of acute respiratory distress syndrome with subsequent respiratory failure associated with interstitial pulmonary fibrosis in the busulfan studies.

Tabulated summaries of adverse events

Adverse reactions reported both in adults and paediatric patients as more than an isolated case are listed below, by system organ class and by frequency. Within each frequency grouping, adverse events are presented in order of decreasing seriousness.

SYSTEM ORGAN CLASS	FREQUENCY	ADVERSE REACTION
Infections and infestations	Frequent	Rhinitis, pharyngitis
Blood and lymphatic system disorders	Frequent	Neutropenia, thrombocytopenia, anaemia, febrile neutropenia, pancytopenia
Immune system disorders	Frequent	Allergic reaction
Endocrine disorders	Frequency unknown	Hypogonadism**
Metabolism and nutrition disorders	Frequent	Anorexia, hyperglycaemia, hypocalcaemia, hypokalaemia, hypomagnesaemia, hypophosphatemia, hyponatraemia
Psychiatric disorders	Frequent	Anxiety, depression, insomnia, confusion

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	Less frequent	Delirium, nervousness, hallucination, agitation
Nervous system disorders	Frequent	Headache, dizziness
	Less frequent	Seizure, encephalopathy, cerebral haemorrhage
Eye disorders	Frequency unknown	Cataract, corneal thinning, lens disorders***
Cardiac disorders	Frequent	Tachycardia, dysrhythmia, atrial fibrillation, cardiomegaly, pericardial effusion, pericarditis
	Less frequent	Ventricular extrasystoles, bradycardia
Vascular disorders	Frequent	Hypertension, hypotension, thrombosis, vasodilatation
	Less frequent	Femoral artery thrombosis, capillary leak syndrome
Respiratory, thoracic and mediastinal disorders	Frequent	Dyspnoea, epistaxis, cough, hiccup, hyperventilation, respiratory failure, alveolar haemorrhages, asthma, atelectasis, pleural effusion
	Less frequent	Hypoxia
	Frequency unknown	Interstitial lung disease**

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Gastrointestinal disorders	Frequent	Stomatitis, diarrhoea, abdominal pain, nausea, vomiting, dyspepsia, ascites, constipation, anus discomfort, oesophagitis, ileus, hematemesis
	Less frequent	Gastrointestinal haemorrhage
	Frequency unknown	Tooth hypoplasia**
Hepato-biliary disorders	Frequent	Hepatomegaly, jaundice, veno occlusive liver disease*
Skin and subcutaneous tissue disorders	Frequent	Rash, pruritus, alopecia, skin desquamation, erythema, pigmentation disorder
Musculoskeletal and connective tissue disorders	Frequent	Myalgia, back pain, arthralgia
Renal and urinary disorders	Frequent	Dysuria, oliguria, haematuria, moderate renal insufficiency
Reproductive system and breast disorders	Frequency unknown	Premature menopause, ovarian failure**
General disorders and administration site conditions	Frequent	Asthenia, chills, fever, chest pain, oedema, oedema general, pain, pain or inflammation at injection site, mucositis
Investigations	Frequent	Increased transaminases, increased bilirubin, increased gamma-glutamyl-transferase, increased alkaline phosphatases, increased weight,

		abnormal breath sounds, elevated creatinine, increased blood urea nitrogen (BUN), decreased ejection fraction.

*veno occlusive disease is more frequent in paediatric population

** reported in post marketing with IV busulfan

***reported in post marketing with oral busulfan

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reactions Reporting Form**", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8

4.9 Overdose

The principal toxic effect is profound myeloablation and pancytopenia but the central nervous system, liver, lungs, and gastrointestinal tract may also be affected.

There is no known antidote to busulfan other than haematopoietic progenitor cell transplantation. Treatment is symptomatic and supportive.

Dialysis has been used twice and should be considered in the case of an overdose. Since, busulfan is metabolised through conjugation with glutathione, administration of glutathione might be considered.

It must be considered that overdose of busulfan will also increase exposure to DMA. In humans the principal toxic effects were hepatotoxicity and central nervous system (CNS) effects. CNS changes precede any of the

more severe side effects. No specific antidote for DMA overdose is known. In case of overdose, management would include general supportive care.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacological classification: A 26 Cytostatics

Mechanism of action

Busulfan is a cytotoxic agent and a bifunctional alkylating medicine in which two labile methanesulphonate groups are attached to the opposite end of a four-carbon alkyl chain. In aqueous media, release of the methanesulphonate groups produces carbonium ions which can alkylate DNA, thought to be an important biological mechanism for its cytotoxic effect.

5.2 Pharmacokinetic properties

The pharmacokinetics of busulfan has been investigated. The information presented on biotransformation and elimination is based on oral busulfan.

Absorption

The pharmacokinetics of intravenous busulfan was studied in 124 evaluable patients following a 2-hour intravenous infusion for a total of 16 doses over four days. Immediate and complete availability of the dose is obtained after intravenous infusion of busulfan. Similar blood exposure was observed when comparing plasma concentrations in adult patients receiving oral and intravenous busulfan at 1 mg/kg and 0,8 mg/kg respectively. Low inter (CV=21 %) and intra (CV=12 %) patient variability on busulfan exposure was demonstrated through a population pharmacokinetic analysis, performed on 102 patients.

Distribution

Terminal volume of distribution V_z ranged between 0,62 and 0,85 l/kg.

Busulfan concentrations in the cerebrospinal fluid are comparable to those in plasma although these concentrations are probably insufficient for anti-neoplastic activity.

Reversible binding to plasma proteins was around 7 % while irreversible binding, primarily to albumin, was about 32 %.

Biotransformation

Busulfan is metabolised mainly through conjugation with glutathione (spontaneous and glutathione-S-transferase mediated). The glutathione conjugate is then further metabolised in the liver by oxidation. None of the metabolites is thought to contribute significantly to either efficacy or toxicity.

Elimination

Total clearance in plasma ranged 2,25 – 2,74 ml/minute/kg. The terminal half-life ranged from 2,8 to 3,9 hours. Approximately 30 % of the administered dose is excreted into the urine over 48 hours with 1 % as unchanged busulfan.

Elimination in faeces is negligible. Irreversible protein binding may explain the incomplete recovery. Contribution of long- lasting metabolites is not excluded.

Linearity

The dose proportional increase of busulfan exposure was demonstrated following intravenous busulfan up to 1 mg/kg.

Compared to the four times a day regimen, the once-daily regimen is characterized by a higher peak concentration, no drug accumulation and a wash out period (without circulating busulfan concentration) between consecutive administrations. The review of the literature allows a comparison of PK series performed either within

the same study or between studies and demonstrated unchanged dose-independent PK parameters regardless the dosage or the schedule of administration. It seems that the recommended intravenous busulfan dose administered either as an individual infusion (3,2 mg/kg) or into 4 divided infusions (0,8 mg/kg) provided equivalent daily plasma exposure with similar both inter-and intrapatient variability. As a result, the control of intravenous busulfan AUC within the therapeutic windows is not modified and a similar targeting performance between the two schedules was illustrated.

Pharmacokinetic/pharmacodynamic relationships

The literature on busulfan suggests a therapeutic AUC window between 900 and 1500 µmol/L.minute per administration (equivalent to a daily exposure between 3600 and 6000 µmol/L.minute). During clinical trials with intravenous busulfan administered as 0,80 mg/kg four-times daily, 90 % of patients AUCs were below the upper AUC limit (1500 µmol/L.minute) and at least 80 % were within the targeted therapeutic window (900-1500 µmol/L.minute). Similar targeting rate is achieved within the daily exposure of 3600 - 6000 µmol/L.minute following the administration of intravenous busulfan 3,2 mg/kg once daily.

Special populations

Hepatic or renal impairment:

The effects of renal dysfunction on intravenous busulfan disposition have not been assessed. The effects of hepatic dysfunction on intravenous busulfan disposition have not been assessed. Nevertheless the risk of liver toxicity may be increased in this population.

No age effect on busulfan clearance was evidenced from available intravenous busulfan data in patients over 60 years.

5.3 Preclinical safety data

Busulfan is mutagenic and clastogenic. Busulfan was mutagenic in *Salmonella typhimurium*, *Drosophila*

melanogaster and barley. Busulfan induced chromosomal aberrations *in vitro* (rodent and human cell) and *in vivo* (rodents and humans). Various chromosome aberrations have been observed in cells from patients receiving oral busulfan.

Busulfan belongs to a class of substances which are potentially carcinogenic based on their mechanism of action. On the basis of human data, busulfan has been classified by the IARC as a human carcinogen.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Dimethylacetamide

Macrogol 400

6.2 Incompatibilities

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

Do not use polycarbonate syringes with Accoran.

6.3 Shelf life

18 months

From a microbiological point of view, the medicinal product should be used immediately. If not used immediately, in use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than the below mentioned conditions when dilution has taken place in controlled and validated aseptic conditions.

- 8 hours (including infusion time) after dilution when stored at or below 25 °C.
- 15 hours after dilution when stored between 2 °C – 8 °C followed by 3 hours stored at or below 25 °C (including infusion time).

6.4 Special precautions for storage

Unopened vials:

Store in a refrigerator (2°C - 8°C) in the closed original packaging.

Do not freeze the diluted solution.

For storage conditions after reconstitution and dilution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

Accoran is a clear, colourless solution free from visible particles. Accoran is packed in a clear 10 ml glass vial (type I) with grey rubber stopper and sealed with aluminium purple flip-off seal packed in an outer carton.

Pack size: 1 vial.

6.6 Special precautions for disposal and other handling

Procedures for proper handling and disposal of anticancer drugs should be followed.

Caution should be exercised in handling and preparing the solution. The use of gloves is recommended as skin reactions may occur with accidental exposure. If this occurs, wash the skin or mucosa immediately and thoroughly with water

Preparation of dilution

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Accoran must be diluted with 0,9 % sodium chloride or 5 % glucose solution for injection. The quantity of the diluent must be 10 times the volume of Accoran to ensure the final concentration of busulfan remains at approximately 0,5 mg/ml.

For example, for a 70 kg (actual body weight) patient, the amount of drug to be administered will be calculated as follows:

(70 kg patient) X (0,8 mg/kg)/ 6 mg/ml) = 9,3 ml Accoran (56 mg total dose).

To prepare the final solution for infusion, add 9,3 ml of Accoran to 93 ml of diluent 0,9 % sodium chloride or 5 % dextrose solution for injection) as calculated below:

(9,3 ml Accoran X (10) = 93 ml of either diluent plus the 9,3 ml Accoran to yield a final concentration of busulfan of 0,5 mg/ml (9,3 ml X 6 mg/ml/ 102,3 ml = 0,5 mg/ml).

All transfer procedures require strict adherence to aseptic techniques, preferably employing a vertical laminar flow safety hood while wearing gloves and protective clothing.

Using a syringe fitted with a needle remove the calculated volume of Accoran from the vial and dispense the content of the syringe into an intravenous bag (or syringe) which already contains the calculated amount of diluent, making sure that the drug flows into and through the solution. Do not put Accoran into an IV bag that does not contain diluent. Always add Accoran to the diluent, not the diluent to Accoran. Mix thoroughly by inverting several times.

Do not use polycarbonate syringes with Accoran.

The entire prescribed dose should be administered over two hours. Prior to and following each infusion, flush the catheter line with approximately 5 ml a of the diluent Do not flush residual medicine in the administration tubing as rapid infusion of Accoran is not recommended.

Do not infuse concomitantly with another IV solution.

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7. HOLDER OF CERTIFICATE OF REGISTRATION

Accord Healthcare (Pty) Ltd

Building 2, Tuscany Office Park,

6 Coombe Place

Rivonia

Johannesburg

South Africa

8. REGISTRATION NUMBER(S)

52/26/1000

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

24 November 2020

10. DATE OF REVISION OF THE TEXT

TBC