

# An Open Label Clinical Study to Evaluate the Safety and Gastrointestinal Tolerance (Product Compliance) of Maxvida® Advance in Hospitalized Patients Requiring Isocaloric Formula for Enteral Tube Feeding

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## Abstract

**Introduction:** Nutrition therapy is of utmost importance in hospitalized patients to meet their energy requirements and overcome the risk of underfeeding. Underfeeding can result in increased hospital length of stay and an increase in the incidence of infections and organ failure. It is thereby associated with a high risk of mortality. To overcome the issue of underfeeding, enteral nutrition is preferred over parenteral nutrition since it can be started within 24-48 hours of hospital admission of the patient. The objective of this study was to evaluate the safety and gastrointestinal tolerance of Maxvida® Advance in hospitalized patients who require isocaloric formula for enteral tube feeding. The gastrointestinal tolerance was evaluated on the basis of Gastric Residual Volume (GRV) >500 ml, diarrhea-free days reduction in stomach irritation, regurgitation, abdominal bloating and vomiting. Safety was determined on the basis of adverse events profile of the supplement. **Methodology:** In this open-label, clinical investigator-initiated clinical study, which was conducted between 24<sup>th</sup> Sep 2020 and 8<sup>th</sup> Nov 2020, at Navin Hospital, Ghaziabad. Maxvida® Advance, a nutritional supplement was administered to hospitalized patients. The participants were recruited based on their informed consent, and the exclusion criteria comprised individuals below 18 years of age or those with any evidence of organ dysfunction or severe clinical deterioration. Maxvida® Advance was administered at a dosage of 45 g in 170 ml water (final volume 200 ml) for two feeds per day and was continued for five days. The GRV and BMI of the participants along with their serum albumin levels, and any incidents of gastrointestinal intolerance were recorded at each day during the study period. **Results:** Ten male and five female participants were included with an average age ranging from 24 to 78 years (median 46.0). Their mean weight, height, and BMI were 61.47 kg, 162.05 cm, and 22.8 kg/m<sup>2</sup>, respectively. Oral carcinoma and mandibulectomy were the most common reasons for advanced enteral feeding among these participants. Other medical conditions included asthma, sepsis, cellulitis/abscess, anemia, and breast cancer. It was observed that all the participants of the study had a good tolerance of the nutrition supplement since their GRV was within the limit of 500 ml for all the study days. The administration of Maxvida® corresponded with a greater number of diarrhea-free days with only 2 reports of diarrhea during the 5-day period. There were no reports of vomiting/nausea associated with the use of Maxvida® Advance during the study period. However, 4 reports of stomach irritation, and 3 reports each of regurgitation and abdominal bloating were made. None of the subject reported adverse events were assessed by investigator as related to Maxvida® Advance. The changes in BMI and serum albumin levels of the participants were not clinically significant ( $p>0.05$ ). No unexpected adverse events were noted with the use of the product, and only mild side effects such as headache and gastritis were observed. **Conclusion:** Based on the results of current study, Maxvida® Advance was concluded

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to be a safe and well-tolerated nutritional supplement, which can be prescribed in adult hospitalized patients at an appropriate dosage.

**Keywords:** Gastrointestinal tolerance; Mandibulectomy; Enteral tube feeding; Maxvida® Advance

## Introduction

Malnutrition is a significant issue affecting approximately 33.6% of the hospitalized patients. [1] It often remains underdiagnosed and undertreated resulting in poor clinical outcomes such as increase in the risk of infections, poor healing of wounds, increased length of stay at the hospital, especially in intensive care units as well as increase in the number of days that require mechanical ventilation of the patient. [2,3] Nutritional support of hospitalized patients has been effective in reducing the rates of morbidity and mortality among patients suffering from malnutrition. Despite the available nutritional guidelines and recommendations, it has been observed that protein and energy requirements of hospitalized patients are being poorly met.

Enteral and parenteral nutrition are used for fulfilling these nutritional requirements of hospitalized patients who are intolerant to an oral diet. They help to provide the essential amounts of micronutrients and macronutrients like proteins meeting the daily energy requirements of hospitalized patients. Enteral nutrition has several advantages over parenteral nutrition since it helps in the preservation of mucosal architecture reducing the risk of inflammation, gut leakage and infections due to the pathogenicity of gut microbiota. [4] It also helps in preserving the hepatic and pulmonary immune function. Enteral feeding has shown to reduce the length of hospital stay and minimize the need for mechanical ventilation in these patients. It must be started within the first 24 to 48 hours of hospital admission in order to improve their feed tolerance and reduce the risk of intestinal barrier dysfunction and infection. [3,5-7] Even in critically ill patients, the use of enteral feeding within 24 hours of hospital admission has a protective effect. [8] Hence, enteral feeding forms the mainstay of early nutrition in hospitalized patients. It helps to lower the risk of morbidity and mortality in hospitalized patients by modulating their immune response and improving their capability of acting against oxidative stress in the body. [9]

Despite the several advantages of enteral nutrition, in critically ill patients, tube feeding is generally not tolerated and may result in side effects such as nausea and vomiting. [10] Further, high volumes of gastric residual through the enteral route of nutrition ease the colonization of bacteria in the gastrointestinal tract increasing the risk of aspiration and complications such as ventilator-associated pneumonia. [11] Thus, it is important to study the impact of enteral feed on the gastric reserve volume of patients before its use in hospitalized patients. The primary objective of this study is to evaluate the safety and gastrointestinal tolerance of Maxvida® Advance, which is a complete nutritional formula for enteral feeding. It contains the desired composition of macro and micronutrients to meet the protein and energy requirements of hospitalized patients and overcome the existing losses. The secondary objective of this clinical study is to ascertain the changes in BMI levels

and serum bilirubin levels of the patients following enteral feeding with Maxvida® Advance. Since Maxvida® Advance is an isocaloric nutritional supplements, side effects occurring due to excessive calculated nutritional requirements in critically ill patients are estimated to be lesser when compared with the use of other nutritional supplements.

## Methodology

### Study design

This was an open-labeled, investigator-initiated clinical study, which was performed to evaluate the safety and gastrointestinal tolerance of Maxvida® Advance in hospitalized patients that required isocaloric formula for enteral tube feeding. It was conducted between 24<sup>th</sup> Sep 2020 and 8<sup>th</sup> Nov 2020, at Navin Hospital, Ghaziabad. Both male and female participants were recruited for a time period of 2 days to 5 days or the period of end of hospitalization depending on which event occurred earlier in an individual participant.

Prior to the selection of the participants, relevant details such as their demographic information and previous medical history were recorded.

To determine the gastrointestinal tolerance of the product, the number of diarrhea-free days, reports of stomach irritation, regurgitation, abdominal bloating and vomiting were evaluated along the analysis of their Gastric Reserve Volume (GRV). GRV was noted at 0730 hrs, 0900 hrs, 1530 hrs and 1700 hrs in each of the participants. The changes in weight, BMI and serum albumin levels were analyzed to determine their overall impact on the clinical parameters of the patient. To determine the safety of the product, the numbers of adverse events were recorded throughout the study.

### Inclusion criteria

The study comprised of hospitalized patients above the age of 18 years who were selected on the basis of their informed consent as signed by their legally acceptable representatives. The inclusion criteria were that the participants must be able to tolerate enteral feeding and must have a nutritional requirement of isocaloric formula for tube feeding.

### Exclusion criteria

Exclusion criteria comprised individuals below 18 years of age, and patients with evidence of organ dysfunction or severe clinical deterioration such as a history of renal, hepatic, cardiovascular, respiratory, skin, hematological, endocrine, neurological or gastrointestinal diseases. Level of deviation from the normal physical or clinical determinants was evaluated to define their exclusion criteria. Those who were receiving tube feeding prior to hospitalization or those who presented with a known allergic reaction to any of the clinical constituents of Maxvida® Advance were also excluded.

## Intervention

For the purpose of this study, Maxvida® Advance was administered at a dosage of 45 g in 170 ml water for 2 days to 5 days or the duration of hospital admission of the patient depending upon the earlier event. It was administered twice daily in the form of enteral tube feeding. The final volume of the feed was kept at 200 ml wherein 1 kcal of energy was achieved in 1 ml solution of Maxvida® Advance. Along with the nutritional supplement, 350 ml of kitchen feed was administered to the participants at 1000 hrs, 1200 hrs and 2000 hrs in order to meet their caloric requirements. The kitchen feed also contained 1 kcal per ml.

## Investigations performed

Investigations such as Complete Blood Count (CBC) and Erythrocyte Sedimentation Rate (ESR) were performed in individuals who were selected following the inclusion and exclusion criteria of the study. Along with this, biochemical investigations such as total bilirubin values, Aspartate aminotransferase (AST), Alanine Transaminase (ALT), serum creatinine, blood urea, fasting blood glucose levels, serum electrolytes, lipid profile and urinalysis were performed. Changes in BMI levels and serum albumin values of the participants in the pre-intervention and post-intervention period of the study were also recorded.

## Data analysis

Data was analyzed with the help of SPSS software to evaluate the safety and tolerance profile of Maxvida® Advance. Statistical tools such as t-test analysis were used to determine the clinical significance of the results.

## Results

The study included 15 male and female participants above 18 years of age who were admitted to the hospital owing to their respective medical histories. There were 10 male and 5 female participants within the age group of 24 to 78 years. Approximately, 60% of the participants were in the age group of 30 to 50 years. The mean weight, height, and BMI of the participants at baseline were 61.47 kg, 162.05 cm, and 22.8 kg/m<sup>2</sup> respectively.

Oral carcinoma and mandibulectomy were the most medical conditions among the participants of this study receiving advanced enteral feed. Other medical conditions observed among these participants included asthma, sepsis, cellulitis/abscess, anemia, and breast cancer.

## Gastrointestinal tolerance of Maxvida® Advance

There were no reports of gastrointestinal intolerance on day 2 of the study. Day 4 and day 5 of the study period had the maximum number of gastrointestinal complaints [Figure 1].

### Vomiting

It was observed that none of the participants suffered from nausea or vomiting at any day during the study period indicating a good gastrointestinal tolerance profile of the product.

### Diarrhea-free days

During study period, only 2 subjects reported diarrhea with their respective complains being at day 1 or day 3 [Table 1]. Remainders of the days were diarrhea free days for all the participants of the study.

### Stomach irritation

There were 4 reports of stomach irritation among the participants of the study with 1 report being on day 1, and day 4 respectively, and 2 reports on day 5. There were no other reports of stomach irritation among the remainder of participants at any point during the study. Hence, the product was concluded to be well-tolerated.

### Regurgitation of food

There were 4 reports of regurgitation of food among the participants subjects with 3 complaints being at day 4 and 1 being on the fifth day [Table 1]. All other subjects well tolerated the product without any significant reports of regurgitation.

### Abdominal bloating

There were 3 reports of abdominal bloating with 2 subjects presenting with the complaint at day 4 and 1 complaint on day 5. All other subjects tolerated the study product without any reports of abdominal bloating though the study period.

**Table 1. Summary of gastrointestinal complaints among the participants of the study.**

Gastrointestinal tolerance parameter	Overall incidence	Day-wise occurrence				
		Day 1	Day 2	Day 3	Day 4	Day 5
Vomiting	0%	-	-	-	-	-
Diarrhea	13.33%	6.66%	-	6.66%	-	-
Stomach irritation	26.66%	6.66%	-	-	6.66%	13.33%
Regurgitation	26.66%	-	-	-	20.00%	6.66%
Abdominal bloating	20.00%	-	-	-	13.33%	6.66%

**Table 2. Mean GRV of the participants during the 5-day period of the study.**

	Mean	Standard deviation
GRV Day 1	198.16	79.58
GRV Day 2	178.58	76.55
GRV Day 3	172.71	89.66
GRV Day 4	115.08	113.75
GRV Day 5	91.25	116.16

### Gastrointestinal reserve volume

The GRV of the research participants was below 500 ml throughout the study period [Table 2].

### Changes in BMI during the study period

The average weight of the participants at the end of the study (day 5) was 59.47 kg. Their average BMI was 22.24, and the average height was 163.33 cm. However, the change in weight and BMI of the participants were not statistically significant ( $p < 0.3343$ ).

### Changes in serum albumin levels during the study period

There was a slight increase in serum albumin levels from 3.5 g/dL at the beginning of the study (day 1) to 3.6 g/dL at the end (day 5). However, this change was statistically insignificant ( $p < 0.4558$ ).

### Adverse events

There were no reports of hematological adverse events during the study period. Overall, 10 adverse events were reported, which were resolved within the hospitalization period of the patient. All of these side effects were mild in nature and did not have an impact on the physical outcomes of the patients. There were 4 cases were of gastritis, 2 cases of dizziness, 1 case of headache, 1 case of fever with rigor and 1 case each of vomiting and nausea. None of the reported adverse events were associated to the use of the nutritional supplement as stated by the investigator.

## Discussion

Using the isocaloric formula for enteral feeding, Maxvida® Advance is associated with a good gastrointestinal tolerance and safety profile of hospitalized patients as per the results of this study. It did not increase the GRV; hence, there were no reports of infections or severe complications that could increase the risk of mortality in any of the participants of the study. [12] The use of Maxvida® Advance caused no episodes of nausea or vomiting among any of the participants throughout the duration of the study (5 days or earlier depending on the hospitalization of the patient). Hence, it did not result any major gastrointestinal

complications. [13] It resulted in mild gastrointestinal impacts such as diarrhea, stomach irritation, abdominal bloating and regurgitation in 13.33%, 26.66%, 20.0% and 26.66% of the participants respectively. These impacts were most profound of the fourth and fifth day of hospitalization [Figure 1]. The changes in BMI and serum bilirubin levels of the participants were not found to be clinically significant ( $p < 0.05$ ).

Enteral nutrition is an effective method of providing nutrition to specific patient groups such as individuals with sepsis or acute pancreatitis, which formed the patient population selected for this study. [14,15] It is also used for fulfilling the nutritional requirements of individuals with head, neck and oral cancer who cannot receive an oral feed thereby reducing their length of hospital stay. [16,17] Enteral feeding maintains the function and integrity of the gut barrier by increasing the production of immunoglobulins, which helps in reducing the risk of infections.

The use of isocaloric formula for enteral feeding in ICU patients helps to overcome the inadequacies of protein-energy imbalance, which can result in an acute inflammatory response in patients. [18] In a prospective observational study of 93 patients, it was found that the maintenance of protein energy balance in malnourished hospitalized patients helps in lowering the levels of C-reactive protein and reducing the risk of inflammation. Further, the maintenance of protein-energy balance helped in reaching the nutritional goals of the patients earlier. Since Maxvida® Advance contains high quality proteins and has an isocaloric formula, it is suitable for meeting the energy needs of hospitalized patients with lower risks of errors during feed calculation that arise due to the difficulty of applying indirect calorimetry to determine the resting energy expenditure of hospitalized patients. [19] Maxvida® Advance is thereby suitable for fulfilling the nutritional requirements of malnourished hospitalized patients.

The issues with gastrointestinal tolerance including diarrhea, abdominal bloating, stomach irritation and regurgitation, as identified in this clinical study, are common side effects of enteral feeding, which are not necessarily associated with the type of feed. [20-23] Diarrhea is a common side effect of enteral feeding observed in 30% to 80% of hospitalized patients. The cause of diarrhea and other types of gastrointestinal issues in

Continous GI Tolerance (Product Complaine)

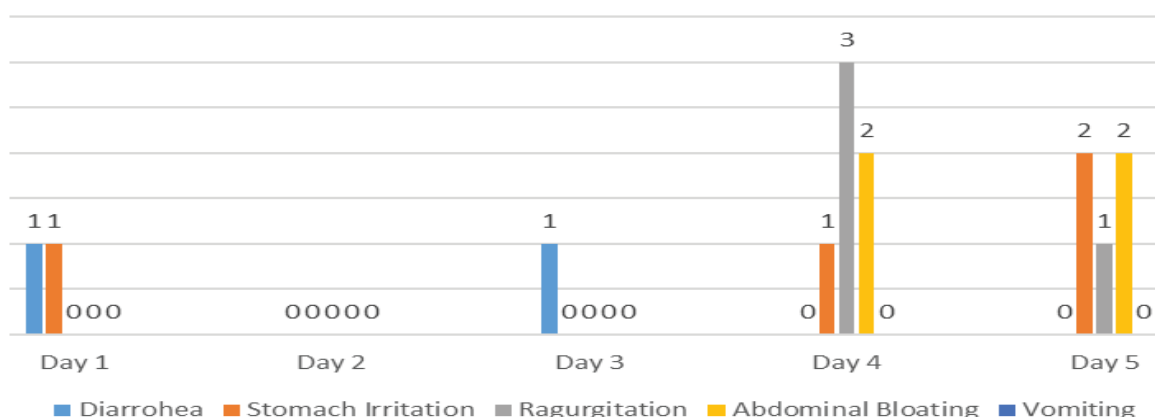


Figure 1: Overall gastrointestinal tolerance or product compliance of Maxvida® Advance.



## Contraindications of enteral tube feeding

- High risk for non-occlusive bowel necrosis
- Active shock or ongoing resuscitation
- Persistent mean arterial pressure (MAP) < 60 mmHg
- Increasing requirement for vasoactive support to maintain MAP >60 mmHg
- Generalized peritonitis
- Intestinal obstruction
- Surgical discontinuity of bowel
- Paralytic ileus
- Intractable vomiting or diarrhea refractory to medical management
- Known or suspected mesenteric ischemia
- Major GI bleeding
- High output uncontrolled fistula

**Figure 2:** Contraindications of enteral feeding.

patients receiving oral feeds has been attributed to the concurrent use of antibiotics and other types of treatments in them. [24] Its incidence in the present study was only 13.33% indicating a good gastrointestinal tolerance profile of Maxvida® Advance. Its superiority to other types of enteral feeds can be attributed to its lactose-free formula since lactose intolerance was the main cause of gastrointestinal intolerance of most enteral feeds.

Although the use of Maxvida® Advance did not result in any significant improvements in the weight status of the patients, it had an overall positive impact on their treatment outcomes since no major clinical complications, mortalities or adverse events were associated with its use in the present study. In a retrospective cohort study of 777 hospitalized patients, it was found that positive relationship between enteral feeding and survival of the patients is not mediated by the BMI or weight status of the patients. [25] Similarly, although it did not have a significant impact on serum bilirubin levels, early administration of enteral feeds with precisely calculated energy requirements has been found to have a protective effect on liver function.

Overall, enteral nutrition with Maxvida® Advance is a safe and effective treatment recommendation for the management of hospitalized patients with mild malnutrition. [26] It does not result in any major safety concerns or adverse events, which supports its use. However, in patients with severe malnutrition or critically illness such as chronic liver disease, parenteral source of nutrition must be opted. Several contraindications of enteral feeding have been outlined in the literature [Figure 2]. Hence, enteral tube feeding with Maxvida® Advance or any other supplements must also be avoided in these patients to avert the possible risks such as worsening of the clinical outcomes of the patient, treatment complications, infections or mortality. [27]

## Limitations of the study

One of the primary limitations of the study is its small

sample size, which reduces the applicability of the results of the research to the actual population. Further, it was a single centre, non-randomized, non-placebo controlled study and the duration of treatment was not clearly defined. The study also did not have a sufficient follow up period, so, the long-term clinical impacts of the use of Maxvida® Advance as an enteral tube supplement in these patients remain unknown. Hence, it is recommended to conduct a large-scale randomized clinical trial before prescribing the use of this isocaloric enteral tube feed in different patient populations.

## Summary

The findings of this open label clinical study of 15 hospitalized patients conclude that Maxvida® Advance is a safe and efficacious supplement for enteral tube feeding. It did not result in an increase in the GRV of the patients, and was not associated with major adverse events such as infections or treatment complications. Although there were episodes of diarrhea, abdominal bloating, stomach irritation and regurgitation in less than 30% of the patients, these normal gastrointestinal complaints are commonly encountered in hospitalized patients. Overall, Maxvida® Advance had a good gastrointestinal treatment profile and can be used in hospitalized patients who are not critically ill. In critically ill or severely malnourished patients, the use of parenteral nutrition must be preferred to avoid the risk of severe nausea and vomiting. Large-scale clinical trials must be conducted before prescribing the use of this nutritional supplement in different populations of hospitalized patients.

## Author Contributions

All named authors for this manuscript meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship. All authors take full responsibility for the integrity of the work and have given final approval for the published version.

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